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Office of Biostatistics and Epidemiology
Division of Biostatistics (HFM-215)

Statistical Review

DATE: 4/16/2003

FDA NUMBER: sBLA 103780/5010

SPONSOR: *Serono, Inc.*

SUBJECT: *Rebif® (Interferon beta-1a)*

FROM: *Yuan Who Chen, Ph.D.*

THROUGH: *G. Gupta, Ph.D., Branch Chief*
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STATISTICAL REVIEW ISSUES / SUMMARY:

The sponsor's major efficacy analyses in this supplemental submission were based on the 48-week data, which was an extension of the 24-week data that used for the original BLA submission. The statistical claims based on 48-week data were confirmed.

SUMMARY OF STATISTICAL ISSUES:

The original BLA submission, which was reviewed by Drs. Clare Gneeco and Cynthia Rask, was based on 24-week data. The statistical issues addressed in Dr. Gnecco's review were consisted of: 1) center pooling strategy, 2) intent-to-treat analysis population, 3) assumption of Poisson regression model, 4) two outliers for baseline T1 lesion, and 5) one problematic site identified by the sponsor. No new statistical issues were found on the 48-week data. The following summaries of statistical issues for 48-week data are to focus on those addressed in Dr. Gnecco's report.

1. As described in the 24-week report, there were 36 centers from 9 countries that participated in this study. Among these 36 centers, 8 centers had contributed no

more than 6 subjects each. This reviewer has performed un-pooled analysis for the primary and major secondary efficacy endpoints using 48-week data. Analyses for major efficacy endpoints by pooling centers into 3 geographical groups (US, Canada, and Europe) were also conducted. The sponsor's efficacy results were found to be robust based on these analyses with 48-week data.

2. The ITT population should include all patients being randomized. As addressed in Dr. Gnecco's review for 24-week data, only one randomized patient was never treated. The sponsor's 48-week report had included all randomized patients (N=677) as the primary efficacy analysis population.

3. This reviewer performed Wilcoxon rank sum test in order to assess the robustness of Poisson modeling findings. The reported findings for those results from analyzing 48-week data by using Poisson regression method were found to be robust.

4. There were two outliers of the number of baseline T1 lesion. For the purpose of investigating the impact of the two outliers on statistical results for the 48-week data, this reviewer repeated Dr. Gnecco's stratified analyses of endpoints involving T1 lesion counts for the 48-week data. Results from stratified analyses for both 48-week and 24-week data are shown in this report.

5. Major efficacy analyses were also performed with the site #238 excluded. The site #238 was identified as one problematic site during the time period of reviewing original BLA submission. This site contributed 11 (1.6%) patients. Based on results from analyzing 48-week data after excluding site #238, the efficacy claims were found to be robust.

BACKGROUND:

This supplemental BLA was to submit a final study and modified labeling, based on 48-week data, in demonstrating that the superiority of Rebif® 44 mcg SC given three times a week to that of Avonex 30 mcg given once a week by showing that the proportion of patients exacerbation-free would be greater with Rebif® than patients with Avonex after 48 weeks treatment.

In the original BLA submission, efficacy analyses were performed on 24-week data and the results were presented in the sponsor's report dated 3 August 2001. In order to distinguish Rebif® from other products those have been approved by the FDA for orphan drug purposes, the sponsor tried to provide evidence to demonstrate the superiority of Rebif® to Avonex®, a drug for use within the currently approved patient population. Results based on the 24-week data had demonstrated the superiority of Rebif® to the active control, Avonex®. Therefore, Rebif® was approved on March 7, 2002 for the indication of multiple sclerosis (MS), which was based on 24 weeks data. The FDA approval letter included a commitment to submit a final study report based on 48-week results.

SUMMARY OF STUDY #21125:

There was only one pivotal study, ***#21125***, for both the original and the supplemental BLA submissions. The study was an open-label, randomized, multi-center, comparative, parallel-group study comparing the treatment effect of two interferon beta-1a regimens in relapsing-remitting multiple sclerosis.

After the 24-week primary endpoint, patients continued in the study on their assigned study medication until either completed 48 weeks or terminated early. Clinical assessments for safety were performed every 3 months. Patients were seen monthly for MRI for 24 weeks and every 3 months and during potential relapses after Week 24. MRI (T2 only) assessments were performed at Week 48 only. The study was to continue until all patients had completed at least 48 weeks on study.

Efficacy data was obtained through repeated neurological examinations and MRI scans. The same procedures in data collection were implemented for both 24-week data and 48-data. A total of 677 patients were randomized. One patient who was randomized to Avonex® group had received no treatment.

Patient Disposition: Of the 677 patients randomized, 339 patients received Rebif® 44 mcg SC and 338 patients were assigned to Avonex® mcg group. Based on the data from ITT population, the patient disposition at 24-week and 48-week is shown in Table 1. Percentages of patients who completed the study are similar for the two groups (Rebif: 92.6% and Avonex: 93.8%) after 48 weeks.

Table 1. Patient disposition at 24-Week and 48-Week, by Treatment Group

	Rebif 44 mcg SC n (%)	**Avonex 30 mg IM n (%)**
Patients who were randomized	339 (100%)	338 (100%)
Patients who completed		
24 weeks of treatment	322 (95.0%)	326 (96.4%)
48 weeks of treatment	314 (92.6%)	317 (93.8%)
Adverse Event		
24-week	11 (3.2%)	3 (0.9%)
48-week	14 (4.1%)	7 (2.1%)
Lack of efficacy		
24-week	1 (0.3%)	0 (0.0%)
48-week	3 (0.9%)	1 (0.3%)
Patient decision		
24-week	3 (0.9%)	5 (1.5%)
48-week	5 (1.5%)	9 (2.7%)

Reviewer's Comment: Table 1 shows patient dispositions at 24-week and at 48-week for each treatment group. In contrast to 24-week data, patient disposition during the period from 25th week to the end of 48th week had shown the consistency between two treatment groups and over the time. Only approximate 3% patients for each group early terminated

during the second 24 weeks. The percentages of dropout patients at the period of second 24 weeks were similar between two arms for adverse event, lack of efficacy, and patient's decision.

Demographic and Baseline Characteristics: No statistically significant differences were found in demographics, i.e. age, gender and race, between two treatment groups. There were no significant group difference for those baseline characteristics variables, such as time to onset of MS, time since last exacerbation, number of exacerbation within last 12 months before screening visit, number of exacerbation within 24 months before screening, and proportion of patients who received MS treatment within 12 months before study Day 1.

Primary Efficacy Endpoint: The proportion of patients who were exacerbation free after 48 weeks. An exacerbation was defined as the appearance of a new system or worsening of an old symptom attributable to MS, accompanied by a new neurological abnormality or focal neurological dysfunction.

Secondary Efficacy Endpoints: (1) The total exacerbation count per patient, (2) the mean number T2 active lesions per patient per scan, (3) proportion of T2 active scans per patient, (3) proportion of patients with no active T2 lesions, (4) proportion of T2 active scans per patient, (5) proportion of patients with no active T2 lesion, (6) time to first relapse, (7) time to second relapse, (8) relapse severity, (9) change in EDSS, (10) time to disability progression confirmed at 3 and 6 months, (11) proportion of patients developed Nab, and (12) effect of Nab development on proportion relapse-free, relapse count and T2 active lesion count.

Analysis Population: The intent-to-treat (ITT) population was to be the primary analysis population for all clinical and MRI outcomes. The ITT population would include all randomized patients, prior to Week 24 analysis. Based on ITT principle, the numbers of subjects for primary efficacy analysis were the same for both 24-week and 48-week data. The sponsor also defined evaluable patient population used for supportive analyses, which varied between parameters.

Randomization and Sample Size Estimation: The randomization scheme and sample size calculation for 48-week data should be the same as those addressed in 24-week report. In order to reduce the redundancy, please refer to Dr. Gnecco's review for a detailed description of randomization and sample size calculation.

STATISTICAL METHODOLOGY:

All test were two-sided and performed at the significance level of $\alpha = 0.05$. The primary efficacy analysis was performed using a logistic regression analysis with treatment and center as the main factors. A saturated model was fit to the data that included treatment, center and treatment by center interaction. The Wald statistic was used to determine the significance of interaction effect between treatment and center. When the interaction effect was not significant, the main effects model with treatment and center would be used to analyze the primary efficacy endpoint.

All MRI T2 endpoints were analyzed using a nonparametric ANCOVA model to determine a treatment difference adjusting for center and the single baseline covariate. For the ITT population, the analysis of the total exacerbation count per patient during 48 weeks was performed using a Poisson regression model.

Interim Analysis: There was a planned interim analysis specified in the protocol for the purpose of early termination with futility and safety concerns. The interim analysis plan was deleted from the protocol and documented in Amendment 4 (dated November 9, 2000). Therefore, no interim analysis was carried out.

Missing Data Imputation: The approaches to impute missing data for the primary efficacy endpoint and for post-baseline MRI parameters were the same as that used for 24-week data. CBER had previously agreed to both approaches.

Observed Cases Analysis: A number of patients withdrew from treatment during the period of 48 weeks study. There were 25 (7.4%) and 21 (6.2%) treatment dropouts on Rebif® and Avonex®, respectively. The distributions by treatment group for time on treatment (in days) and time on study (in days) are shown in Table 2. This reviewer performed observed cases analysis, which excluded those patients who withdrew from the treatment without any exacerbation occurred. Using the logistic regression method to analyze the data, the p-values were 0.0133 and 0.0105 for un-pooled and pooled centers, respectively. The p-value was 0.0146 obtained by using Fisher's exact test without taking center effect into account.

***Reviewer's Comment*:** Assigning all patients in the Rebif® group to exacerbation and all patients in the Avonex® to exacerbation-free to conduct a worst-case analysis will be too conservative. However, both distributions of time on treatment and time on study are very similar between two treatment groups. The observed cases analyses demonstrated the significance between two groups for the 48-week data. The missing data did not prove to be problematic for the 48-week data.

Table 2. Distributions of Time on Treatment and Time on Study, by Treatment

	Rebifâ 44 mcg SC (N=339)	**Avonexâ 30 mg IM (N=337)**
Time on Treatment (in days)		
Mean ± sd	322.9 ± 57.1	325.4 ± 50.9
Median	337	337
Time on Study (in days)		
Mean ± sd	329.6 ± 43.8	330.5 ± 41.5
Median	337	337

REVIEWER'S EFFICACY ANALYSES:

This reviewer performed the primary analysis with treatment group and pooling center (US, Canada, and Europe) as two main factors in the logistic regression model. The interaction effect between treatment group and center was not statistically significant. With removing the interaction from the model, the treatment was significant with p=0.0147. The primary analysis was also conducted with un-pooled center in the logistic

regression model. It turned out that the treatment group was significant (p=0.0118). In addition, using Fisher's exact test to examine difference between the treatment groups yielded a significant p-value of 0.0161.

Because the 48-week data was a continuation of the 24-week data, analytic results on 48-week data and results on 24-week data are presented in this report in order to evaluate the consistency between the two time points.

For the same reason, the statistical methods and cutoff points reported in Dr. Gnecco's review were used to analyze and report the 48-week data. The results on 24-week data presented in this report were adapted from Dr. Gnecco's review.

***Reviewer's comment*:** In Table 3, the primary efficacy analysis results using the Fisher's exact test for both 48-week data and 24-week data show consistently significant difference between two treatment groups. After excluding site #238, the p-values provide with evidence of significant between groups difference as well.

Table 3. Proportion of Patients Remained Exacerbation Free after 24 Weeks and 48 Weeks, by Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48		
Exacerbation Free	209 (61.7%)	177 (52.4%)
Not Exacerbation Free	130 (38.3%)	161 (47.6%)
Odds Ratio	1.5	
95% CI	(1.1, 2.1)	
p-value	0.0161	
Week 24		
Exacerbation Free	254 (74.9%)	214 (63.3%)
Not Exacerbation Free	85 (25.1%)	124 (36.7%)
Odds Ratio	1.7	
95% CI	(1.2, 2.4)	
p-value	0.0012	

Excluding site #238 from the analysis, the Fisher's exact p-values for 48-week data and 24-week data are 0.0061 and 0.0004, respectively.

This reviewer also conducted ITT analyses by stratifying for age (<38 years vs. ≥38 years) and gender. The two-sided stratified Cochran-Mantel-Haenszel test was used. Table 4 shows the results from primary analysis stratifying for age and Table 5 shows the results stratifying for gender, with and without excluding site #238. Both two tables demonstrate consistent results after stratifying by age and gender.

The same analysis was also conducted with stratifying for geographical region (US, Canada and Europe). Table 6 shows the analysis results from primary analysis stratifying for geographical region, with and without excluding site #238.

***Reviewer's comment*:** All tables 4-6 demonstrate the robustness of the primary efficacy analysis by comparing to results on 24-week data and by stratifying for different demographic parameters.

Table 4. Proportion of Patients remained Exacerbation free after 24 Weeks and 48 Weeks Controlling for Age, by Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48 (Age < 38)		
Exacerbation Free	91 (58.0%)	93 (51.4%)
Not Exacerbation Free	66 (42.0%)	88 (48.6%)
Week 48 (Age ³ 38)		
Exacerbation Free	118 (64.8%)	84 (53.5%)
Not Exacerbation Free	64 (35.2%)	73 (46.5%)
p-value	0.0189	
Week 24 (Age < 38)		
Exacerbation Free	110 (70.1%)	108 (60.0%)
Not Exacerbation Free	47 (29.9%)	72 (40.0%)
Week 24 (Age ³ 38)		
Exacerbation Free	144 (79.1%)	106 (67.1%)
Not Exacerbation Free	38 (20.9%)	52 (32.9%)
p-value	0.0017	

Excluding site #238 from the analyses with 48-week data and 24-week data, the p-values are 0.0068 and 0.0006, respectively.

Table 5. Proportion of Patients Remained Exacerbation Free after 24 Weeks and 48 Weeks Controlling for Gender, by Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48 (Males)		
Exacerbation Free	61 (71.8%)	50 (58.1%)
Not Exacerbation Free	24 (28.2%)	36 (41.9%)
Week 48 (Females)		
Exacerbation Free	148 (58.3%)	127 (50.4%)
Not Exacerbation Free	106 (41.7%)	125 (49.6%)
p-value	0.0140	
Week 24 (Males)		
Exacerbation Free	69 (81.2%)	56 (65.1%)
Not Exacerbation Free	16 (18.8%)	30 (34.9%)
Week 24 (Females)		
Exacerbation Free	185 (72.8%)	158 (62.7%)
Not Exacerbation Free	96 (27.2%)	94 (37.4%)
p-value	0.0011	

Excluding site #238 from the analyses with 48-week data and 24-week data, the p-values are 0.0045 and 0.0003, respectively.

Table 6. Proportion of Patients Remained Exacerbation Free after 24 Weeks and 48 Weeks Controlling for Region, by Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48 (US)		
Exacerbation Free	147 (65.9%)	120 (54.6%)
Not Exacerbation Free	76 (34.1%)	100 (45.4%)
Week 48 (Canada)		
Exacerbation Free	21 (60.0%)	19 (50.0%)
Not Exacerbation Free	14 (40.0%)	19 (50.0%)
Week 48 (Europe)		
Exacerbation Free	41 (50.6%)	38 (47.5%)
Not Exacerbation Free	40 (49.4%)	42 (52.5%)
p-value	0.0147	
Week 24 (US)		
Exacerbation Free	173 (76.2%)	144 (65.5%)
Not Exacerbation Free	50 (23.8%)	76 (44.5%)
Week 24 (Canada)		
Exacerbation Free	24 (68.6%)	24 (63.2%)
Not Exacerbation Free	11 (31.4%)	14 (36.8%)
Week 24 (Europe)		
Exacerbation Free	57 (70.4%)	46 (57.5%)
Not Exacerbation Free	24 (29.6%)	34 (42.5%)
p-value	0.0011	

Excluding site #238 from the analyses with 48-week data and 24-week data, the p-values are 0.0051, and 0.0004, respectively.

Impact of Baseline MRI Lesion on the Primary Efficacy Endpoint: Since two outliers of T1 lesion counts were identified, several stratified analyses to assess the robustness of the primary efficacy analysis were performed by this reviewer. The primary analyses were stratifying for baseline CU count (≤1 vs. >1 and =0 vs. >0), baseline T1 lesion count (≤0 vs. >0) and baseline T2 lesion count (≤0 vs. >0). Table 7 and Table 8 show the results for stratifying for baseline CU count ≤1 vs. >1 and =0 vs. >0, respectively. Table 9 shows the results for the parameter of baseline T1 count ≤0 vs. >0 and Table 10 shows the results for baseline T2 count ≤0 vs. >0. All p-values were obtained from using the two-sided stratified Cochran-Mantel-Haenszel test.

***Reviewer's comment*:** With different baseline MRI parameters and cutoff points, all the above analyses support the statistically significant difference between two treatment groups.

Table 7. Proportion of Patients Remained Exacerbation Free after 24 Weeks and 48 Weeks, by Baseline CU Lesion Count and Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48 (Baseline CU Lesion Count £ 1)		
Exacerbation Free	145 (66.2%)	99 (54.4%)
Not Exacerbation Free	74 (33.8%)	118 (45.6%)
Week 48 (Baseline CU Lesion Count > 1)		
Exacerbation Free	54 (50.9%)	53 (49.1%)
Not Exacerbation Free	52 (49.1%)	55 (50.9%)
p-value	0.0402	
Week 24 (Baseline CU Lesion Count £ 1)		
Exacerbation Free	176 (80.4%)	140 (64.5%)
Not Exacerbation Free	43 (19.6%)	77 (35.5%)
Week 24 (Baseline CU Lesion Count > 1)		
Exacerbation Free	68 (64.2%)	66 (61.1%)
Not Exacerbation Free	38 (35.8%)	42 (38.9%)
p-value	0.0013	

Excluding site #238 from the analyses with 48-week data and 24-week data, the p-values are 0.0148 and 0.0004, respectively.

Table 8. Proportion of Patients Remained Exacerbation Free after 24 Weeks and 48 Weeks, by Baseline CU Lesion Count and Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48 (Baseline CU Lesion Count = 0)		
Exacerbation Free	99 (67.8%)	83 (56.5%)
Not Exacerbation Free	47 (32.2%)	64 (43.5%)
Week 48 (Baseline CU Lesion Count > 0)		
Exacerbation Free	100 (55.9%)	90 (50.6%)
Not Exacerbation Free	79 (44.1%)	88 (49.4%)
p-value	0.0381	
Week 24 (Baseline CU Lesion Count = 0)		
Exacerbation Free	116 (79.5%)	96 (65.3%)
Not Exacerbation Free	30 (20.5%)	51 (34.7%)
Week 24 (Baseline CU Lesion Count > 0)		
Exacerbation Free	128 (71.5%)	110 (61.8%)
Not Exacerbation Free	51 (28.5%)	68 (38.2%)
p-value	0.0012	

Excluding site #238 from the analyses with 48-week data and 24-week data, the p-values are 0.0149 and 0.0012, respectively.

Table 9. Proportion of Patients Remained Exacerbation Free after 24 Weeks and 48 Weeks, by Baseline T1 Lesion Count and Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48 (Baseline T1 Lesion Count £ 0)		
Exacerbation Free	124 (66.7%)	97 (54.5%)
Not Exacerbation Free	62 (33.3%)	81 (45.5%)
Week 48 (Baseline T1 Lesion Count > 0)		
Exacerbation Free	75 (54.0%)	76 (51.7%)
Not Exacerbation Free	64 (46.0%)	71 (48.3%)
p-value	0.0439	
Week 24 (Baseline T1 Lesion Count £ 0)		
Exacerbation Free	149 (80.1%)	114 (64.0%)
Not Exacerbation Free	37 (19.9%)	64 (36.0%)
Week 24 (Baseline T1 Lesion Count > 0)		
Exacerbation Free	95 (68.3%)	92 (62.6%)
Not Exacerbation Free	44 (31.7%)	55 (37.4%)
p-value	0.0014	

Excluding site #238 from the analyses with 48-week data and 24-week data, the p-values are 0.0172 and 0.0005, respectively.

Table 10. Proportion of Patients Remained Exacerbation Free after 24 Weeks and 48 Weeks, by Baseline T2 Lesion Count and Treatment Group (ITT population)

	Rebif® 44 mcg SC (N=339) n (%)	**Avonex® 30 mg IM (N=338) n (%)**
Week 48 (Baseline T2 Lesion Count £ 0)		
Exacerbation Free	130 (64.7%)	50 (58.1%)
Not Exacerbation Free	71 (34.3%)	36 (41.9%)
Week 48 (Baseline T2 Lesion Count > 0)		
Exacerbation Free	69 (55.7%)	59 (49.2%)
Not Exacerbation Free	55 (44.3%)	61 (50.8%)
p-value	0.0368	
Week 24 (Baseline T2 Lesion Count £ 0)		
Exacerbation Free	157 (78.1%)	136 (66.3%)
Not Exacerbation Free	44 (21.9%)	69 (33.7%)
Week 24 (Baseline T2 Lesion Count > 0)		
Exacerbation Free	87 (70.2%)	70 (58.3%)
Not Exacerbation Free	37 (29.8%)	50 (41.7%)
p-value	0.0011	

Excluding site #238 from the analyses with 48-week data and 24-week data, the p-values are 0.0136 and 0.0003, respectively.

Secondary Efficacy Endpoint: This reviewer performed analyses for major secondary endpoints, such as time to first and second exacerbation during 48 weeks of treatment, mean number of T2 active lesions per patient per scan, proportion of T2 active scans per patient, proportion of patients with no T2 active lesion during 48 weeks. The sponsor's analytic results were confirmed.

Exacerbation Count Endpoint: A nonparametric Wilcoxon rank sum test was used to analyze the exacerbation count endpoint in order to assess the robustness of Poisson regression modeling results. A p-value of 0.0231 was obtained for the comparison of the exacerbation counts of the two treatment groups. It demonstrated the robustness of the results from Poisson regression modeling.

Change in EDSS Score from Baseline to 48 Weeks: Wilcoxon rank sum test was used to examine the group difference of change in EDSS score from baseline to 48 weeks. It yielded a non-significant p-value of 0.2659.

Efficacy Analyses on Second Half of Study: Three efficacy analyses on the second 24 weeks ITT data were provided by the sponsor dated 7 April 2003. Those included proportion of exacerbation free, exacerbation count by 6-month interval, and mean number of T2 lesions per patient per scan. Based on the table provided by the sponsor, the primary efficacy outcome, proportions of exacerbation free patients, for each of 24 weeks by treatment group are shown as below:

Table 11. Proportion of Exacerbation Free Patients (ITT Population)

	Rebif® 44 mcg SC (N=339) n/n (%)		**Avonex® 30 mg IM (N=338) n/n (%)**	
	0-24 Weeks	**24-48 Weeks**	**0-24 Weeks**	**24-48 Weeks**
Exacerbation Free	254/339 (74.9%)	207/254 (81.5%)	207/338 (63.3%)	175/214 (81.8%)
Not Exacerbation Free	85/339 (25.1%)	47/254 (18.5%)	124/338 (36.7%)	39/214 (18.2%)

Table 11 shows that the proportions of exacerbation free patients for 24-48 weeks period were almost identical. It was the same to exacerbation count by 6-month interval for 24-48 weeks.

***Reviewer's comment*:** Although no analyses were performed for 24-48 weeks data, the 24-48 weeks data provided with important information that the proportions of exacerbation free patients of the two treatment groups were very similar. It should be considered to include the information of Table 11 in labeling.

SUMMARY AND CONCLUSIONS:

Based on the 48 weeks data, this reviewer's analyses of the major efficacy endpoints confirm the sponsor's major efficacy results.